Remarks

Claims 1-19, 24 and 25 are currently pending in the application, claims 20-23 are withdrawn from consideration. Claims 1-3, 5, 9-12, 14, 16, 18, 19, 24, and 25 are currently amended; claims 20-23 are withdrawn-currently amended. No new matter has been added. The present amendments result in the exclusion of particular compounds. Given the extensive disclosure of alternatives at all of the positions shown in the disclosed compounds in the specification, combined with the previously presented claim 1 having exclusion of sub-genera, as well as particular species, it is clear that Applicants were in possession of the exclusion of the compounds. Accordingly, Applicants submit that no new matter has been added to the application and that all new claims are fully supported by the specification.

Support for the amended claims claims can be found throughout the specification. Examples of support for the amended claims appear at the following page numbers and paragraph numbers that are referenced with respect to U.S. Patent Application Publication 2005/0215645 A1 of the above-referenced application:

Amended claims 1and 2

Definition of R^5, see page 21, paragraph [0230].

Amended claim 3

Definition of Z, see page 21, paragraph [0235];

→ a methylene group was selected.

Amended claim 5

Definition of R^1, the recitation "a group represented by the formula -X-A wherein A represents hydrogen atom or an acyl group, X represents oxgen atom or NH," was selected from amended claim 1.

Amended claim 10

Four compounds were deleted because these compounds were excluded by the restriction of the scope of amended claim 1.

Amended claim 11

6-Acetylamino-N-benzylnaphthalene-1-sulfonamide and 6-amino-N-benzylnaphthalene-1-sulfonamide were deleted because these compounds were excluded by the restriction of the scope of claim 10.

Amended claim 14

Definition of Z, see page 21, paragraph [0235]

→Methylene group was selected.

Amended claim 16

Definition of R^1; the phrase "a group represented by the formula –X-A wherein A represents hydrogen atom or an acyl group, X represents oxgen atom or NH," was selected from amended claim 2.

Amended claim 18

6-Acetylamino-N-benzylnaphthalene-1-sulfonamide and 6-amino-N-benzylnaphthalene-1-sulfonamide were deleted because these compounds were excluded by the restriction of the scope of claim 1.

Amended claims 21, 23 and 24

Definition of R^5, see page 21, paragraph [0230].

Response To The Office Action

Information Disclosure Statements

Applicants note with appreciation the Examiner's indication that the Information Disclosure Statements filed on June 20, 2006, April 14, 2005, and January 18, 2005 have been considered. Furthermore, Applicants note that a Third Supplemental Information Disclosure Statement has been submitted concurrently with this response

Priority

The Office Action acknowledges Applicants' claim of priority under 35 U.S.C. §119 and 365 and indicates that a certified copy of the priority document was received by the Office.

Restriction Requirement

Applicants note that the Examiner had previously restricted the claims based upon an alleged lack of unity of invention. With the present amendment, Applicants note that claims 20-23 have been amended, and respectfully submit that these claims share a "special technical feature" as defined in the PCT Unity of Invention rules. In particular, Applicants note that all of the pending claims share the requirement of a substances categorized by the general formula in claim 1.

In the Restriction Requirement dated February 1, 2006, the Examiner relied on compounds categorized as formula (I) of U.S. Patent No. 5,707,985 to McKenzie et al. (McKenzie). With the present amendment, none of the pending claims reads on any compound in McKenzie.

In view of the present amendments and remarks, Applicants respectfully submit that all of the claims satisfy the requirements for unity of invention and that the withdrawn claims should be rejoined. Thus, Applicants respectfully request that the Examiner reconsider and withdraw the Restriction Requirement.

Rejections under 35 U.S.C. § 112

Claims 1-9 and 12-19 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter. The Office Action bases this rejection on an allegedly improper Markush group listing.

In response, Applicants submit that by the above amendment to claims 1 and 12, the claimed compounds are now listed in the alternative. Therefore, Applicants respectfully request withdrawal of this rejection.

Claims 1-10, 12-19, and 24-35 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter. The Office Action asserts this rejection because of a typographical error in claim 1, which inadvertently lists moieties R^5 twice, instead of reciting moieties R^5 and R^6.

Applicants submit that this error has been corrected by the above amendment and respectfully request withdrawal of this rejection.

Claims 1-10, 12-19, and 24-35 are rejected under 35 U.S.C. § 112, first paragraph, because the Office Action alleges that the specification, while being enabling for enhancing the reduction in the survival rate of Jurkat cells when the compounds of the instant invention are administered with bleomycin, does not reasonably provide enablement for treating any cancer.

In response, Applicants traverse this rejection. Applicants emphasize that the present claims are directed towards enhancing the effect of a cancer therapy. Furthermore, the present claims specify that the cancer therapy is based on a mode of action of DNA injury. Antitumor agents such as bleomycin, adriamycin, cisplatin, cyclophosphamide, or mitomycin C are well known to target DNA and have a similar mode of action. These agents target the DNA of cancer tissue and tumors and cause an injury to this target DNA. Examples of such injuries include cleaving of the target DNA and/or crosslinking the complementary strains of the target DNA. As a result, the target DNA is prevented from further proliferation and the cancer tissue and tumors stops in growing followed by degeneration (apotosis).

The compounds claimed in the present invention enhance the suppressing effect on the proliferation of tumor cells by bleomycin, as well as other antitumor agents. Therefore, someone of ordinary skill in the art would know that the same compounds can be administered with other DNA-targeting antitumor agents, since the suppression of DNA proliferation is desired for the treatment of any cancer.

The Office Action asserts that *the artisan using the invention would be a physician with an MD degree and several years of experience*. Furthermore, the Examiner asserts that *there are certain drugs for certain cancers* and that one skilled in

the art be able to determine which existing drugs are likely to be useful for treating a tumor. However, the Examiner alleges that the application has not fully determined which tumors will and will not respond to the treatment with the instantly claimed compounds.

Applicants respectfully traverse this argument. The artisan, i.e., a physician with several years of experience, is well aware of the mode of action of drugs that are used for treating a certain tumor. That is, the physician would know that an antitumor agent such as bleomycin and any of the other above-mentioned agents target the DNA of cancer tissue and tumors as described above. When informed of the present invention, the physician would also know that administering one of the claimed compounds would support the treatment, i.e., suppression of cancer DNA proliferation benefits the mode of action of the DNA targeting drug.

Furthermore, the aforementioned class of antitumor agents targeting DNA of cancer tissues and tumors are known to have antitumor effect not only on Jurkat cells but on other types of tumor cells. For example, see Jpn. J. Cancer Res., 80, pp.83-88, which was submitted in the Information Disclosure Statement of January 18, 2005. In order to further inform the Office regarding drugs that have anticancer activity on cells other than Jurkat cells, Applicants respectfully submit The Merck Manual of Diagnosis and Therapy, 17th edition, pp. 986-985 in. Therefore, one of ordinary skill in the art would readily understand that the compounds of the present invention can enhance antitumor actions of the above-mentioned class of DNA-targeting antitumor agents on a variety of antitumor cells including Jurkat cells.

In addition, Applicants note that radiation therapy also induces DNA injury, which results in suppression of tumor cells, for example, see Endocrine-Related Cancer, 6, pp. 41-44, 1999. Accordingly, one of ordinary skill in the art would readily understand that the compounds of the present invention can enhance the antitumor efficacy of radiotherapy in view of the present application.

Applicants respectfully submit that the enablement requirement is satisfied. Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102(b)

The Office Action rejects claims 1-10, 12-17, 24, and 25 under 35 U.S.C. § 102 as being anticipated by at least one of the following references:

(a) Marsilje et al., Bioorganic & Medicinal Chemistry Letters, 2000, 10, pp. 477-481, compound 2v on page 478;

(b) Stein et al., J. Med. Chem., 1995, 38, pp. 1344-1354, compound 71 on page 1347; and

(c) Butenas et al., Biochemistry, 1992, 31, 5399-5411, allegedly disclosing 5-amino-naphtalene-1-sulfonyl-benzamide.

Although the cited documents do not disclose compounds of general formula (I) in claim 1 as medicaments for enhancing an effect in cancer therapy, Applicants note that by the foregoing amendments, the claims have been amended to expressly exclude the

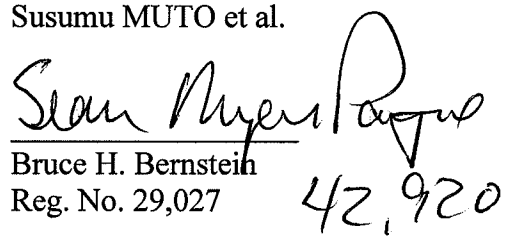
compounds cited by the Office Action. Therefore, Applicants respectfully submit that this rejection is rendered moot and withdrawal of the rejection is respectfully requested.

Conclusion

Reconsideration of the outstanding Office Action and allowance of the present application and all the claims therein are respectfully requested and now believed to be appropriate.

Should the Examiner have any further comments or questions or if any issues remain which can be expeditiously resolved by a telephone conference, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully Submitted,
Susumu MUTO et al.



Bruce H. Bernstein
Reg. No. 29,027 42,920

October 5, 2007
GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191

Endocrine-Related Cancer (1999) **6** 41-44

Induction of cell death by radiotherapy

G M Ross

Academic Radiotherapy Unit, Institute of Cancer Research and Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK

Abstract

Ionising radiation remains one of the most effective tools in the therapy of cancer. It combines the properties of an extremely efficient DNA-damaging agent with a high degree of spatial specificity. Nonetheless, there remain considerable differences in the outcome for treatment of tumours of differing histological type treated by radiotherapy. Tumours arising from lymphoid or germ cells are significantly more radiocurable than most solid tumours of epithelial origin. The molecular mechanisms underlying such differences in cellular radiosensitivity are the subject of current research. When normal mammalian cells are subjected to stress signals - e.g. radiation, chemotherapeutic drugs, oxygen deficiency - a range of gene products involved in the sensing and signalling of such stresses are activated. The response of eukaryotic cells to ionising radiation includes activation of DNA repair pathways and cell cycle checkpoints, with subsequent full 'biological' recovery or cell death. Radiation induces two different modes of cell death termed mitotic or clonogenic cell death, and apoptosis. Until recent years, there was surprisingly little mechanistic understanding of the events following induction of physical damage by radiation and biological outcome for the cell. There have been recent major advances in our understanding of the signal transduction pathways involved in determining the fate of cells after irradiation.

Endocrine-Related Cancer (1999) **6** 41-44

Induction and fate of DNA damage by ionising radiation

Photons generated by clinical linear accelerators for therapy induce a range of biochemical lesions in genomic DNA, thought to be the most important subcellular target molecule. The class of lesion whose fate most closely correlates with cell death is the DNA double strand break (dsb), which can be induced by direct ionisation of DNA or indirectly via the generation of free radicals. The majority of lesions are repaired rapidly by highly conserved enzymatic pathways. Misrepaired lesions, due to 'structural' repair of breaks without fidelity of the genetic message, lead to mutation, with possible change of cell phenotype. Frank unrepaired breaks may generate chromosomal aberrations. Subsequent cell death may occur after a variable number of cell cycles (Fig. 1). This mode of cell death is exhibited by most non-haematopoietic cell lineages in response to ionising radiation, and is referred to as mitotic or clonogenic cell death. It is considered to be the major mechanism by which the majority of solid tumours respond to clinical radiotherapy.

The correlation between the amount of mitotic cell death, DNA lesion induction and chromosomal aberrations suggests that this pattern of cell death probably results from failure of cells to completely or accurately repair DNA damage. Recent work in mammalian and yeast model systems suggests that at least two distinct pathways involving some four discrete complexes facilitate the repair of dsbs. In one such pathway, so-called non-homologous recombinational repair, little or no homology of DNA sequence is required for rejoining of breaks. The DNA-dependent protein kinase (DNA-PK) and the RAD50 complex act predominantly during G1/early S phase. By contrast, in homologous recombination extensive homology is required between the region of DNA with a dsb and the repair template. This pathway requires the RAD52 complex, acting mainly at late S/G2, or the breast cancer predisposition genes BRCA1/2 complex, acting in S phase (for review see Hendrickson (1997)).

Apoptosis is an alternative mode of cell death after irradiation, but appears to be preferentially expressed in embryonal and haematopoietic cells, with significantly lower levels of induction in epithelial cell types. Radiation-induced apoptosis was initially considered not to require cell division, and therefore regarded as a form of death expressed in interphase cells. Further investigation revealed that it could be induced readily in the cells of the small intestine, lymphocytes and salivary glands

1351-0088/99/006-041

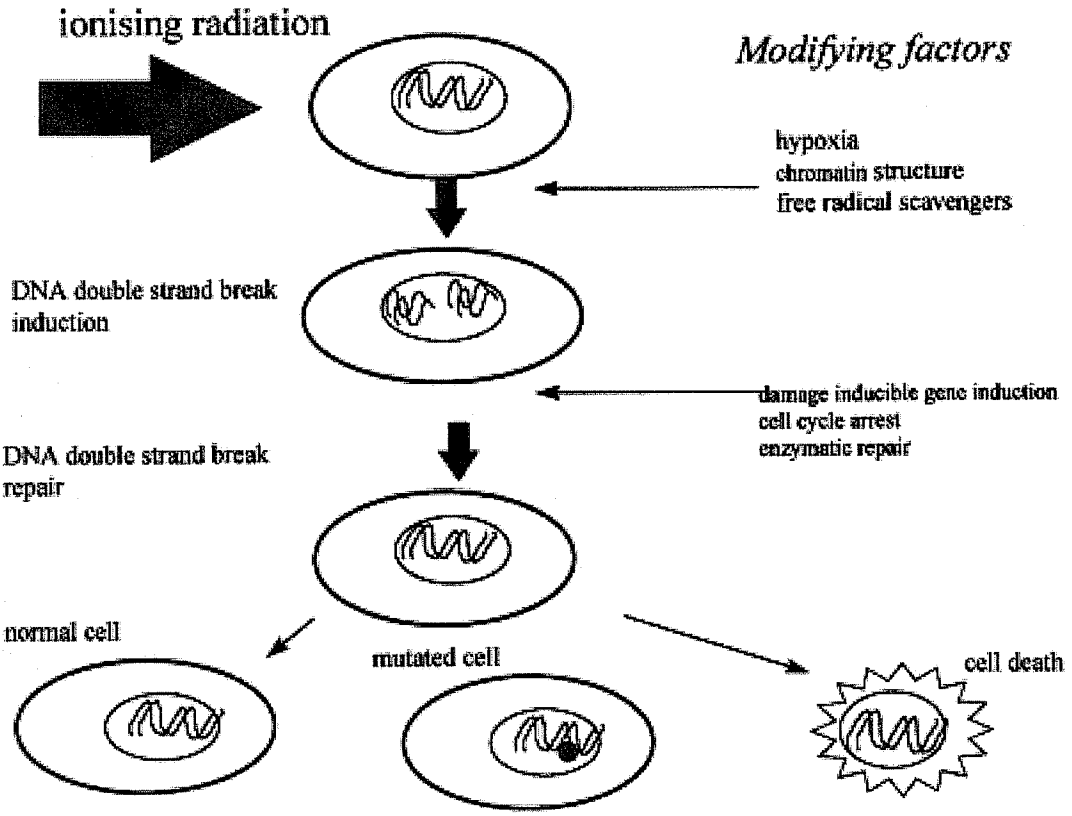


Figure 1 Radiation induced damage to genomic DNA, thought to be the most important subcellular target molecule.

and in experimental tumour systems (Nomura *et al.* 1992, Hendry *et al.* 1995). Given the apparently low levels of radiation-induced apoptosis in the cell types which give rise to most solid human cancers, its relevance to the determination of the response in clinical radiotherapy has been questioned. Studies quantitatively correlating apoptosis events with loss of clonogenic cell survival in non-haematopoietic cells have suggested that the major pathway leading to cell death is mitotic rather than apoptosis. Necessarily many of these data relate to outcomes observed in cell lines. Some mouse tumours treated *in vivo* demonstrate correlations between radiosensitivity and the amount of spontaneous or induced apoptosis.

Clinical regression of solid tumours after completion of therapy is observed over many months, whereas treatment of lymphoid tumours can result in dramatic regression during a course of treatment, perhaps offering circumstantial evidence that cell lineage might be a major determinant of the mode of cell death in response to radiotherapy. This does not preclude a contribution of spontaneous and induced apoptosis in solid tumours to treatment outcome; however, there is a paucity of clinical data to indicate the true contribution of apoptosis to radiosensitivity (Dewey *et al.* 1995).

Signal transduction of the radiation response and the DNA damage surveillance network

Recently it has been recognised that the cell membrane may be important as a target for at least one pathway of radiation-induced apoptosis (Santana *et al.* 1996). Ionising radiation activates sphingomyelinase, which catalyses the hydrolysis of sphingomyelin to the lipid second messenger, ceramide, thereby inducing interphase death by apoptosis. This pathway has been demonstrated to be deficient in the lymphoblasts of patients with Niemann-Pick disease, a condition in which there is an inherited lack of acid sphingomyelinase. *In vitro*, radiosensitivity can be restored by retroviral transfer of human acid sphingomyelinase cDNA.

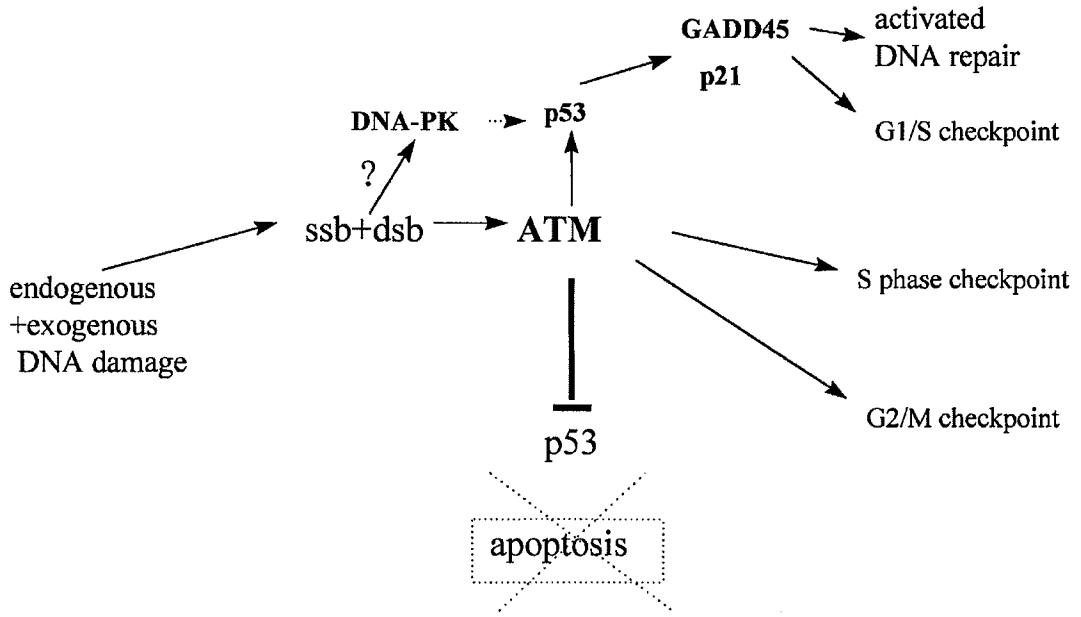


Figure 2 The DNA damage surveillance network.
ssb, single strand DNA breaks

Although the cell membrane is a target for some forms of radiation-induced apoptosis, the nucleus is also a critical target. A major pathway of radiation-induced apoptosis involves DNA damage and subsequent induction of a range of genes including ataxia telangiectasia (AT) and p53 (Fig. 2). In the presence of DNA damage, p53-dependent gene transcription is increased and ubiquitin-dependent degradation of the protein is blocked leading to induction of apoptosis and/or cell cycle arrest. Activation of p53 is mediated via stress-activated protein kinases. In its latent state p53 cannot bind DNA, and it requires phosphorylation to function as a transcription factor. Recent data suggest that DNA-PK is required for the p53 response (Woo *et al.* 1998). DNA-PK modifies the amino-terminal region of p53, which controls its interaction with the transcriptional apparatus and with MDM2. In lymphocytes isolated from p53 knockout mice, clonogenic cell survival is dramatically modulated by inactivation of the p53 response. Expression of a retrovirally transferred mutant p53 transgene in the human ovarian tumour line A2780 produced a significant but lesser increase in radiation resistance, in comparison with the control A2780 cells with an intact p53 response (McIllwrath *et al.* 1994). However, clinical studies examining the relationship between clinical radiosensitivity and tumour p53 status have largely failed to demonstrate a significant effect.

The AT gene is emerging as another key participant in the cellular response to ionising radiation (Meyn 1995). The phenotype of the rare autosomal recessive disorder ataxia telangiectasia is complex, but key clinical features include progressive cerebellar degeneration, oculocutaneous telangiectasias, immunodeficiency, premature ageing and lymphoreticular malignancies. One per cent of the population is estimated to be heterozygous, with a possible increased risk of solid tumours. Several studies have shown an increased incidence of breast cancer in AT heterozygotes, with a relative risk estimated to be 3.9 (Easton 1994). The AT gene was cloned in 1995, and is 150 kb in length spread over 66 exons. A 13 kb mRNA transcript contains an open reading frame of 9168 bp encoding a 350 kDa nuclear protein (Savitsky *et al.* 1995). Mutations have been detected in over 100 AT patients; over 80% result in truncation of the protein. The similarity of the phenotypes suggests that most of the mutations are functionally equivalent. Sequence comparisons between human mutated in ataxia telangectasia (ATM) and mouse ATM suggest that the gene is a member of a family of genes involved in cell cycle regulation (TOR1, TOR2, MEC1 of *Saccharomyces cerevisiae* and rad3 of *S. pombe*), telomere length monitoring (TEL1 of *S. cerevisiae*), meiotic recombination (MEC1 of *S. cerevisiae* and mei41 of *Drosophila melanogaster*) and DNA repair (DNA-PK), supporting a key role for ATM in

DNA dsb repair and cell cycle regulation. *In vitro*, cells derived from AT heterozygotes demonstrate increased radiosensitivity in comparison with normal individuals, as measured by chromosomal damage (Chen *et al.* 1994). However, as yet there is no clinical evidence that such individuals have abnormal clinical responses to radiotherapy.

A role for BRCA1 and BRCA2 in the radiation response?

Although analysis of the nucleotide sequence of BRCA1 and BRCA2 failed to yield insight into the likely functions of these genes, recent data have provided compelling evidence for a role in DNA damage response pathways, including the response to ionising radiation (Zhang *et al.* 1998). Both proteins are co-regulated in the cell cycle and associate with human RAD51, the eukaryotic equivalent of the bacterial recombination protein, recA, which is involved in repair of dsbs and chromosome maintenance. The first indirect evidence for a role of BRCA2 in DNA repair was the observation that disruption of BRCA2 in embryos produced ionising radiation hypersensitivity. Direct biochemical evidence for an involvement of the BRCA2 gene product in DNA repair comes from the observation that embryonic fibroblasts isolated from mice bearing a truncating mutation in BRCA2 appear to have altered kinetics in the rejoining of DNA dsb as measured in the single cell gel electrophoresis assay (Connor *et al.* 1997). These mice show a remarkable similarity to Atm-deficient mice, namely, growth retardation (*in vitro* and *in vivo*), absence of mature gametes and shortened lifespan due to the development of thymic lymphoma (Barlow *et al.* 1996). This similarity could indicate a role for both genes in the same DNA damage response pathway, either directly involved in repair, or via low level overexpression of p53 induced by failure of repair. In support of this hypothesis, the growth failure of Atm null fibroblasts is rescued in a p53 null background. We await evidence that the Atm-/- background can rescue the BRCA2 phenotype. Significant questions remain as to the potential relevance of haploid insufficiency in ATM and BRCA2 and implications for cancer predisposition and response to DNA-damaging therapy.

Summary

Knowledge is rapidly increasing of the pathways involved in determining cell fate after exposure to ionising radiation. Many of the genes involved play key roles in genomic stability, and may even participate in determining cancer proneness. Hopefully some of these gene products will provide new targets for therapeutic modulation of the radiation response and facilitate rational molecular radio-sensitisation.

References

Barlow C, Hirotsune S, Paylor R, Liyanage M, Eckhaus M, Collins F, Shiloh Y, Crawley JN, Ried T, Tagle D & Wynshaw-Boris A 1996 Atm-deficient mice: a paradigm of ataxia telangiectasia. *Cell* **86** 159-171.

Chen P, Farrell A, Hobson K, Girjes A & Lavin M 1994 Comparative study of radiation-induced G2 delay and chromatin damage in families with ataxia telangiectasia. *Cancer Genetics and Cytogenetics* **76** 43-46.

Connor F, Bertwistle D, Mee PJ, Ross GM, Swift S, Grigorieva E, Tybulewicz VLJ & Ashworth A 1997 Tumorigenesis and a DNA repair defect in mice bearing a truncating mutation in Brca2. *Nature Genetics* **17** 423-430.

Dewey WC, Ling CC & Meyn RE 1995 Radiation-induced apoptosis: relevance to radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* **33** 781-796.

Easton D 1994 Cancer risks in A-T heterozygotes. *International Journal of Radiation Biology* **66** S177-S182.

Hendrickson EA 1997 Cell cycle regulation of mammalian DNA double strand break repair. *American Journal of Human Genetics* **61** 795-800.

Hendry JH, Potten CS & Merritt A 1995 Apoptosis induced by high LET and low LET radiations. *Radiation and Environmental Biophysics* **34** 59-62.

McIllwrath A, Vasey PA, Ross GM & Brown R 1994 Cell cycle arrests and radiosensitivity of human tumour cell lines: dependence on wild-type p53. *Cancer Research* **54** 3718-3722.

Meyn MS 1995 Ataxia telangiectasia and cellular responses to DNA damage. *Cancer Research* **55** 5991-6001.

Nomura T, Kinuta M & Hongyo T 1992 Programmed cell death in whole body and organ systems by low dose radiation. *Journal of Radiation Research* **33** 109-123.

Santana P, Pena LA, Haimovitz-Freidman A, Martin S, Green D, McLoughlin M, Cordon-Cardo C, Schuchman EH, Faks Z & Kolesnick R 1996 Acid sphingomyelinase-deficient human lymphoblasts and mice are defective in radiation-induced apoptosis. *Cell* **86** 189-199.

Savitsky K, Sfez S, Tagle DA, Ziv Y, Sartiel A, Collins FS, Shiloh Y & Rotman G 1995 The complete sequence of the coding region of the ATM gene reveals similarity to cell cycle regulation in different species. *Human Molecular Genetics* **4** 2025-2032.

Woo RA, McClure KG, Lees-Miller SP, Rancourt DE & Lee PWK 1998 DNA-dependent protein kinase acts upstream of p53 in response to DNA damage. *Nature* **394** 700-704.

Zhang H, Tombline G & Weber BL 1998 BRCA1, BRCA2 and DNA damage response:collision or collusion? *Cell* **92** 433-436.

genetic techniques are glycoproteins that have antitumor and antiviral activity, which may originate partially from immunologically mediated mechanisms. Depending on the dosage, IFNs may either enhance or decrease cellular and humoral immune functions and may affect macrophage and NK cell activity. IFNs also inhibit division and certain synthetic processes in a variety of cells. Human clinical trials have indicated that IFNs have antitumor activity in hairy cell leukemia, chronic myelocytic leukemia, and AIDS-associated Kaposi's sarcoma. Some responsiveness has been seen to a lesser degree in non-Hodgkin's lymphoma, multiple myeloma, and ovarian carcinoma. However, IFNs are quite toxic; patients may develop fever, malaise, leukopenia, alopecia, and myalgia.

Bacterial adjuvants (eg, attenuated tubercle bacilli [BCG]), extracts of BCG (eg, methanol-extracted residue), or killed suspensions of *Corynebacterium parvum* have been used in randomized trials. They have been used with or without added tumor antigen to treat a broad variety of cancers, usually along with intensive chemotherapy or radiotherapy. Direct injection of BCG into melanoma nodules almost always leads to regression of the injected nodules and, occasionally, of distant, noninjected nodules. Intravesicular instillation of BCG in patients with superficial bladder carcinoma has prolonged disease-free intervals, possibly as a result of immunologic mechanisms. Some studies suggest that methanol-extracted residue may help prolong drug-induced remission in acute myeloblastic leukemia and that BCG added to combination chemotherapy may increase survival in patients with ovarian carcinoma and possibly with non-Hodgkin's lymphoma. However, many studies have shown no benefit.

144 / PRINCIPLES OF CANCER THERAPY

Successful treatment of cancer requires elimination of all cancer cells, whether at the primary site, extended to local-regional areas, or metastatic to other regions of the body. The major modalities of therapy are surgery and radiotherapy (for local and local-regional disease) and chemotherapy (for systemic sites). Other important methods include endocrine therapy (for selected cancers, eg, prostate, breast, endometrium, liver), immunotherapy (biologic response modifiers to enhance endogenous immune cell kill and tumor vaccines), and thermotherapy (cryotherapy and heat). Multimodality therapy combines the assets of each of these.

Clinical definitions of oncologic terms help clarify the goals and progress of therapy. For a potential cure, a **complete remission** or **complete response** must be achieved, which requires disappearance of clinically evident disease. Such patients may appear to be cured but may still have viable neoplastic cells that will, in time, cause relapse. A **partial response** is a > 50% reduction in the size of a tumor mass or masses; a partial response may lead to significant palliation and prolongation of life, but tumor regrowth is inevitable. A patient may also have **no response.**

The interval between disappearance of cancer and relapse is termed the **disease-free interval** or **disease-free survival.** Similarly, the **duration of response** is the time from partial response to the time of overt progression. **Survival** is the time from diagnosis to death.

SURGERY

Surgery is the oldest form of effective cancer therapy. Curative surgery requires that the tumor be localized or have limited local-regional spread, which allows en bloc resection. This is particularly applicable to cancer of the bladder, breast, cervix, colon, endometrium, larynx and head and neck, kidney,

TABLE 144–1. FIVE-YEAR DISEASE-FREE SURVIVAL RATES FOR CANCER THERAPY

Therapy	Site	Stage	5-yr Disease-Free Rate (%)
Surgery (single modality)	Cervix	I	94
	Breast	I	82
	Bladder	0 + A	81
		B_1	66
	Colon	A	81
		B	64
		C	27
	Prostate	A + B	80
	Larynx	I + II	76
	Endometrium	I	74
	Ovary	I	72
	Oral cavity	I + II	67–76
	Kidney	I + II	67
	Testis (nonseminomatous)	I	65
	Lung (non–small cell)	I	50–70
		II	37
Radiotherapy (single modality)	Non-Hodgkin's lymphoma (nodular)	Pathologic stage I	60
	Non-Hodgkin's lymphoma (diffuse)		90
	Hodgkin's disease	Pathologic stage IA	88
		Pathologic stage IIA	83
		Pathologic stage IIIA	71
	Testis (seminoma)	II + III	84
	Prostate	A + B	80
		C	67
	Larynx	I + II	76
	Cervix	II + III	60
	Nasopharynx	I, II, III	35
	Nasal sinuses	I, II, III	35
	Breast	III	29
	Esophagus		10
	Lung	III_{M0} (excluding Pancoast's tumor)	9
Chemotherapy (single modality)	Choriocarcinoma (women)	All stages	95
	Testis (nonseminomatous)	III	88
	Hodgkin's disease	IIIB + IVA + B	74
	Diffuse large cell lymphoma	II, III, IV	64
	Burkitt's lymphoma	I, II, III	60
	Leukemia (childhood, ANLL)		54
	Leukemia (< 40 yr, ANLL)		50
	Leukemia (> 40 yr, ANLL)		25
	Lung (small cell)	Limited	25
Surgery and radiation	Testis (seminoma)	I	94
	Endometrium	II	62
	Bladder	B_2 + C	54
	Oral cavity	III	36
	Hypopharynx	II + III	33
	Lung	III_{M0} Pancoast	32
Surgery and chemotherapy	Breast	II	62
	Colon	III	70
	Prostate	C	50–68
	Ovary: carcinoma	II, III, IV	30–60
	Ovary: germ cell	II, III, IV	85
Radiation and chemotherapy	CNS (medulloblastoma)		71–80
	Ewing's sarcoma	All stages	70
	Rectum (squamous cell carcinoma)		40
	Lung (small cell cancer)	Limited	16–20
Surgery, radiation, and chemotherapy	Kidney (Wilms' tumor)	All stages	80
	Embryonal rhabdomyosarcoma	All stages	80
	Lung	IIIB	35
	Oral cavity, hypopharynx	III + IV	20–40
	Rectum	II + III	50

*ANLL = acute nonlymphocytic leukemia.

lung, ovaries, and testes. In circumstances in which an en bloc resection cannot be performed, multimodality therapy with radiotherapy, chemotherapy, or chemoradiation may reduce the size of the cancer, making it amenable to surgical resection for cure.

Cancers curable with surgery alone are listed in TABLE 144–1. Detailed issues about surgical treatment are discussed in chapters on cancers of specific organs.

RADIOTHERAPY

Radiotherapy can be delivered by various methods. The most common is external beam with a linear accelerator, which largely delivers photons (γ-radiation). Neutron beam radiotherapy is used for some tumors with a narrow tissue margin. Electron beam radiotherapy has a very short tissue penetration and is best used for skin or superficial cancers. Proton therapy, although limited in availability, can provide very narrow depth of field exposure with sharp margins. Brachytherapy involves placing a powerful radioactive source into the tumor bed itself (eg, in prostate or brain) via needles, thereby providing a very high dose in a small field. Systemic radioactive isotopes can be used for organs that have receptors for their uptake (thyroid cancer) or for palliation of generalized bony sites (ie, radiostrontium for metastatic prostate cancer). Curative radiotherapy generally requires local or local-regional disease that can be encompassed within the radiation field.

Radiation injury to cells is random and nonspecific, with complex effects on DNA. The efficacy of therapy depends on cellular injury beyond the normal capacity of repair. In general, repair of normal tissue is more effective than that of cancer, allowing differential cell kill.

Radiotherapy is curative in many cancers (see TABLE 144–1). Radiotherapy combined with surgery (for head and neck, laryngeal, or uterine cancer) or with chemotherapy and surgery (for sarcomas or breast, esophageal, lung, or rectal cancers) improves cure rates over traditional single-modality therapy. Phototherapy, the newest multimodality approach, uses a porphyrin derivative (a protoporphyrin) to attach to and thereby illuminate the tumor for selected uptake of radiation.

Radiotherapy can provide important palliative control of cancer, even when cure is not possible. Radiotherapy for brain tumors prolongs patient functioning; for cord-compressing cancers, it can eliminate neurologic deficit; for superior vena caval syndromes, it can eliminate abrupt death; and for symptomatic or painful metastases, it usually controls symptoms.

CHEMOTHERAPY

The ideal chemotherapeutic drug would target and destroy only cancer cells without adverse effects or toxicities on normal cells. Unfortunately, no such drug exists; there is a narrow therapeutic index between cell kill of cancer cells and that of normal cells. Despite this, chemotherapy, even with single drugs, has achieved cure in selected cancers (ie, choriocarcinoma, hairy cell leukemia, chronic lymphocytic leukemia). More commonly, multidrug regimens with differing mechanisms, intracellular sites of action, and toxicities (to reduce the potential compounding of toxicity) provide significant cure rates (eg, in acute leukemia, bladder and testicular cancer, Hodgkin's disease, malignant lymphoma, small cell lung cancer, and nasopharyngeal cancer).

The failure of chemotherapy drugs in vivo when efficacy has been documented in vitro has led to extensive studies of drug resistance. One identified mechanism, multidrug resistance, is due to several genes that limit drug dwell and function in cancer cells in the patient. Attempts to alter this resistance have not been successful.

Common effective chemotherapeutic drugs are described in TABLE 144–2.

MULTIMODALITY AND ADJUVANT THERAPY

The limited success of treatment with surgery or radiotherapy alone led to the discovery that surgery combined with radiation can increase the disease-free survival and cure rate in some tumors (eg, gynecologic, lung, laryngeal, and head and neck cancer). Because these modalities focus on local-regional control, chemotherapy is added as an adjuvant to eliminate cancer cells beyond the limited region. **Adjuvant chemotherapy** can increase disease-free survival and cure rate by about 30% in breast cancer in women and men, colon cancer (Dukes' B2 and C), advanced bladder cancer, and ovarian cancer. This success has led to the use of chemotherapy or radiotherapy before surgery, termed **induction (or neoadjuvant) therapy**. This approach has improved survival in inflammatory and advanced breast, lung (eg, stage IIIA and B), nasopharyngeal, and bladder cancers.

OTHER MODALITIES

ENDOCRINE THERAPY

Additive or ablative endocrine therapy can influence the course of some cancers. Endocrine therapy is not curative; it is only palliative. Orchiectomy has significant palliative value in metastatic prostate cancer, commonly prolonging survival 3 to 5 yr. Its efficacy is based on the testosterone-dependent population of prostate cancer cells. Other cancers with hormone receptors on their cells (eg, breast, endometrium, ovary) can often be palliated by hormone ablative therapy. This success led to the use of hormones as pharmacologic therapy for such tumors. Estrogen effectively palliates prostate cancer but increases the risk of heart disease. These observations led to treatment with gonadotropin secretory inhibitors. Leuprolide, a synthetic analog of gonadotropin-releasing hormone, inhibits gonadotropin secretion and resultant gonadal androgen production and is as effective for the palliation of prostate cancer as is orchiectomy. Even more complete androgen blockage can be achieved by adding an oral antiandrogen (flutamide or bicalutamide), which limits androgen binding to its receptor; this combination appears to increase disease-free survival by 6 to 12 mo over leuprolide or orchiectomy alone.

Similarly, estrogen ablation (by oophorectomy) provides palliation in advanced breast cancer. Tamoxifen, an oral hormone, can bind to estrogen receptors on breast cancer cells and is as effective for palliation as is oophorectomy. It is a particularly effective therapy for metastatic breast cancer in the postmenopausal woman. As an adjuvant therapy in breast cancer, it prolongs the duration of disease-free survival, improves cure rate in receptor-positive patients by 20 to 30%, and reduces the risk of contralateral breast cancer by about 60%. For details of endocrine therapy, see TABLE 144–2.

BIOLOGIC RESPONSE MODIFIERS

Interferons, interleukins, and tumor necrosis factor (TNF) are biologic proteins that function in immune (protective) responses. They are synthesized by cells of the immune system when invaded by viruses as a physiologic protective response. In pharmacologic amounts, they have palliative efficacy in some cancers.

Interferons have demonstrated activity in selected cancers. In hairy cell leukemia, complete response rates of 60 to 80% have occurred. In chronic myelogenous leukemia, up to 20% of patients can achieve a complete response (Philadelphia chromosome–negative status). Interferon can prolong disease-free survival (12 to 24 mo) after effective chemotherapy in myeloma and some forms of lymphoma. Survival is somewhat prolonged in patients with melanoma and renal cell cancer. Cosmetic palliation occurs in Kaposi's sarcoma. Significant toxicities of interferon include fatigue, nausea, leukopenia, chills and fever, and myalgias.

Interleukins, primarily the lymphokine interleukin-2 produced by activated T cells, have been used with modest palliative effect in renal cell cancer. Several other interleukins are under study, as is TNF.

HYPERTHERMIA AND CRYOTHERAPY

Heating tumor beds (to 41° C [105.8° F]) to enhance cell kill using drugs or radiation has been tried with only trivial efficacy. Cryosurgery (using a probe directly into the tumor mass) provides modest palliation in liver cancer and inoperable breast cancer.

MANAGEMENT OF ADVERSE EFFECTS

NAUSEA AND VOMITING

Antiemetics prevent or relieve nausea and vomiting, which commonly occurs with radiotherapy to the abdomen and with many chemotherapeutic drugs, especially when

TABLE 144–2. COMMONLY USED ANTINEOPLASTIC DRUGS

Drug Class	Drug	Usual Dosage and Route	Mechanism of Action	Cycle	Commonly Responsive Tumors	Toxicity and Remarks
Alkylating drugs	Mechlorethamine (nitrogen mustard)	6 mg/m² IV	Alkylate DNA with restricted uncoiling and replication of strands	Non-specific	Hodgkin's disease, malignant lymphoma, small cell lung cancer, breast and testicular cancer, chronic lymphocytic leukemia	Alopecia with high IV dosage; nausea and vomiting; myelosuppression; hemorrhagic cystitis (especially with ifosfamide), which can be ameliorated with mesna; mutagenic and leukemogenic; aspermia; permanent sterility (possible)
	Chlorambucil (Leukeran)	4–10 mg/day po				
	Cyclophosphamide (Cytoxan)	600 mg/m² IV 50–200 mg/m² po				
	Melphalan (Alkeran)	1 mg/kg po q 4 wk				
	Ifosfamide (Ifex)	2–4 g/m²/day IV × 3–5 days q 3–4 wk				
Antimetabolites						
Folate antagonist	Methotrexate	2.5–5.0 mg/day po 25–50 mg/1 dose/wk po 100–10,000 mg/m² IV (with rescue)	Binds to dihydrofolate reductase and interferes with (pyrimidine) thymidylate synthesis	S-phase–specific	Choriocarcinoma (female), head and neck cancer, acute lymphocytic leukemia, ovarian cancer, malignant lymphoma, osteogenic sarcoma	Mucosal ulceration; bone marrow suppression; increased toxicity with impaired renal function or ascitic fluid (with pooling of drug); leucovorin rescue can reverse toxicity at 24 h (10–20 mg q 6 h × 10 doses)
Purine antagonist	6-Mercaptopurine	100 mg/m²/day po	Blocks de novo purine synthesis	S-phase–specific	Acute leukemia	Myelosuppression, alopecia
Pyrimidine antagonist	5-Fluorouracil	300–1000/m² IV or continuous infusion	Interferes with thymidylate synthase to reduce thymidine production	S-phase–specific	Gastrointestinal neoplasms, breast cancer	Mucositis, alopecia, myelosuppression, diarrhea and vomiting, hyperpigmentation; significant synergistic effect when given after methotrexate
	Cytarabine	100 mg/m² IV continuous infusion	Inhibits DNA polymerase	S-phase–specific	Acute leukemia (especially non-lymphocytic), malignant lymphoma	Myelosuppression, nausea and vomiting, cerebellar and conjunctival toxicities at high dosage, skin rash
	Gemcitabine (Gemzar)	1200 g/m²/wk IV	Interferes with conversion of dCMP to dUMP, thereby limiting the pool of thymidine available	S-phase–specific	Pancreatic, lung, and bladder cancer	Myelosuppression
Spindle poison (from plants)						
Vincas	Vinblastine (Velban)	0.1–0.2 mg/kg IV q 7–10 days	Arrests mitosis by alteration of microtubular proteins	Metaphase	Lymphomas, leukemias, breast cancer, Ewing's sarcoma, testicular cancer	Alopecia, myelosuppression, peripheral neuropathy, ileus
	Vincristine (Oncovin)	1.4 mg/m² IV*	Same as vinblastine	Metaphase	Same as vinblastine	Peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion
	Vinorelbine (Navelbine)	20 mg/m²/wk IV	Same as vinblastine	Metaphase	Lung and breast cancer	Myelosuppression, neuropathy
	Paclitaxel (Taxol)	135 mg–200 g/mL IV q 3 wk	Promotes assembly of microtubules	G_2 and metaphase arrest	Breast, lung, ovarian, head and neck, and bladder cancer	Myelosuppression, alopecia, myalgia, arthralgia, neuropathy
	Docetaxel (Taxotere)	100 g/m² IV q 3 wk	Promotes assembly of microtubules	G_2 and metaphase arrest	Breast and lung cancer	Myelosuppression, alopecia, skin rash, fluid retention
Podophyllotoxins	Etoposide (VePesid)	100 mg/m²/day IV for 3–5 days 100 mg/day po for 14 days/mo	Inhibits mitosis by unknown mechanisms; inhibits topoisomerase II	Metaphase	Lymphoma, Hodgkin's disease, testicular cancer, lung cancer (especially small cell), acute leukemia	Nausea, vomiting, myelosuppression, peripheral neuropathy; cleared by liver (teniposide by kidney); increased toxicity in renal failure
	Irinotecan (Camptosar)	100–125 g/m²/wk IV	Inhibits topoisomerase I	Non-specific	Colon, rectal, and lung cancer	Diarrhea, myelosuppression, alopecia
	Topotecan (Hycamtin)	1.5 g/m² IV daily × 5 days q 3–4 wk	Inhibits topoisomerase I	Non-specific	Ovarian and lung cancer	Myelosuppression

Table continues on the following page.

TABLE 144–2. COMMONLY USED ANTINEOPLASTIC DRUGS *(Continued)*

Drug Class	Drug	Usual Dosage and Route	Mechanism of Action	Cycle	Commonly Responsive Tumors	Toxicity and Remarks
Antibiotics	Doxorubicin (Adriamycin)	40–75 mg/m² rapidly IV or 30 mg/m²/day for 3 days by continuous IV†	Inhibits uncoiling of DNA by intercalation between DNA strands	Non-specific	Acute leukemia, Hodgkin's disease, other lymphomas, breast and lung cancer	Nausea and vomiting, myelosuppression, alopecia; cardiac toxicity at cumulative dosage > 500 mg/m²; daunomycin, a related derivative, has greater cardiac toxicity; its role has been limited to acute leukemia
	Bleomycin (Blenoxane)	6–15 U/m² sc or IV	Causes incision of DNA strands	Non-specific	Squamous cell cancer, lymphoma, testicular and lung cancer	Anaphylaxis, chills and fever, skin rash; pulmonary fibrosis at dosage > 200 mg/m²; requires renal excretion
	Mitomycin	Usually 10 to 12 mg/m², slowly IV	Inhibits DNA synthesis by acting as a bifunctional alkylator	Not cycle- or phase-specific; effects are maximized if cells are in late G or early S phase	Gastric adenocarcinoma; colon, breast, and lung cancer; transitional cell cancer of the bladder	Local extravasation causes tissue necrosis; myelosuppression, with leukopenia and thrombocytopenia 4 to 6 wk after treatment; alopecia; lethargy; fever; hemolytic-uremic syndrome
Nitrosoureas	Carmustine (BiCNU)	150–200 mg/m² IV q 6 wk	Alkylates DNA with restricted uncoiling and replication of strands	Non-specific	Brain tumors, lymphoma	Myelosuppression, pulmonary toxicity (fibrosis), renal toxicity
	Lomustine (CeeNU)	100–130 mg/m² po q 6 wk	Carbamoylation of amino acids in proteins	Non-specific	Brain tumors, (astrocytoma, glioblastoma)	Myelosuppression (delayed), nephrotoxicity
Inorganic ions	Cisplatin (Platinol)	60–100 mg/m² IV or 20 mg/m² IV daily × 5 days	Intercalation and intracalation between DNA strands inhibits uncoiling of DNA	Non-specific	Lung cancer (especially small cell); testicular, breast, and gastric cancer; lymphoma	Anemia, ototoxicity, nausea, vomiting, peripheral neuropathy, myelosuppression
	Carboplatin (Paraplatin)	300 g/m² or target area under the curve of 5–6 IV q 3 wk	Same as cisplatin	Non-specific	Lung, head and neck, and breast cancer	Myelosuppression
Biologic response modifiers	Interferon (Intron A, Roferon-A)	3–25 × 10^6 U/m² 3 times/wk sc or IV	Antiproliferative effect	Unknown	Hairy cell leukemia, chronic myelogenous leukemia, lymphomas, Kaposi's sarcoma (AIDS), renal cell cancer, melanoma	Fatigue, fever, myalgias, arthralgias, myelosuppression, nephrotic syndrome (rarely)
Enzymes	Asparaginase (Elspar)	1000–6000 U/m² IV or IM	Depletion of asparagine, on which leukemic cells depend	Cycle-specific	Acute lymphocytic leukemia	Acute anaphylaxis, hyperthermia, pancreatitis, hyperglycemia, hypofibrinogenemia
Hormones	Tamoxifen (Nolvadex)	10 mg po bid	Places cells at rest; binding of estrogen receptor	Non-specific	Breast cancer	Hot flushes, hypercalcemia, deep vein thrombosis
	Leuprolide (Lupron)	7.5 mg/mo IM or depot 21 mg IM q 3 mo	Inhibits gonadotropin secretion	Non-specific	Prostate cancer	Hot flushes, decreased libido, irritation at injection site
	Flutamide (Eulexin)	250 mg po q 8 h	Binds the androgen receptor		Prostate cancer	Decreased libido, hot flushes, gynecomastia
	Megestrol acetate (Megace)	160–240 mg/day po	Inhibits estrogen action	Non-specific	Breast and endometrial cancer	Weight gain, fluid retention

*Dose commonly "capped" at a total of 2 mg in adults.
†Higher dosage tolerated when given by continuous IV.
dCMP = deoxycytidine monophosphate; dUMP = deoxyuridine monophosphate.

given in combination. Sometimes the nausea and vomiting is functional (see FUNCTIONAL VOMITING in Ch. 21) or due to the cancer itself. Therefore, the underlying cause should always be sought and corrected.

Stimulation of the vomiting center in the medulla can arise in the chemoreceptor trigger zone (CTZ), cerebral cortex, or vestibular apparatus or can be relayed directly from peripheral areas (eg, gastric mucosa). Antiemetics appear to act in these areas, but their mechanism of action is not well understood. Generally, drug therapy is more successful for prophylaxis than for treatment of nausea and vomiting.

Serotonin-receptor antagonists are the most effective drugs available for the management of nausea and vomiting associated with radiotherapy or chemotherapy and with many disease processes. Virtually no toxicity occurs with granisetron and ondansetron, although headache and, rarely, orthostatic hypotension have occurred with ondansetron. These drugs are first-line antiemetic therapy; their major drawback is expense.

Antidopaminergics include many of the phenothiazines (eg, prochlorperazine, fluphenazine), which appear to act by selectively depressing the CTZ and, to a lesser extent, the vomiting center. These second-line drugs are useful in treating mild to moderate nausea and vomiting. Because most phenothiazines (except thioridazine and mesoridazine) appear to be equally effective if given in sufficient dosage, the choice of drug may depend on consideration of side effects.

Metoclopramide stimulates the motility of the upper GI tract, increases the tone and amplitude of gastric contractions, and increases duodenal and jejunal peristalsis. The result is accelerated gastric emptying and intestinal transit.

Metoclopramide functions as an antiemetic by its gastrokinetic effects and, in addition, appears to have some central dopamine antagonist actions. The most important side effects are extrapyramidal symptoms, which are in part dose-related. Benadryl will protect from these. Other side effects include drowsiness and fatigue. The drug is contraindicated when stimulation of GI motility might be dangerous (mechanical obstruction or perforation), in pheochromocytoma, and in epileptics or in patients receiving other drugs likely to cause extrapyramidal reactions. Its use as an antiemetic has largely been replaced by the serotonin-receptor antagonists.

Dronabinol, Δ-9-tetrahydrocannabinol (THC), is approved to treat nausea and vomiting caused by chemotherapy in patients unresponsive to conventional antiemetic treatment. THC is the principal psychoactive component of marijuana. Its mechanism of antiemetic action is unknown, but cannabinoids bind to opioid receptors in the forebrain and may indirectly inhibit the vomiting center. The drug has largely been abandoned because it has variable oral bioavailability, is ineffective against the nausea and vomiting of platinum-based chemotherapy regimens, and has significant side effects (eg, drowsiness, orthostatic hypotension, dry mouth, mood changes, visual and time sense alterations).

CYTOPENIAS

Anemia, leukopenia, and thrombocytopenia may develop during radiotherapy or chemotherapy. Clinical symptoms and decreased efficacy of radiotherapy occur at Hct levels < 30%. Although packed RBC transfusions are rarely needed, recombinant erythropoietin is used to manage the cancer fatigue and RBC requirement. In general, 100 to 150 U/kg sc three times/wk (a convenient adult dose is 10,000 U) is very effective and has reduced or eliminated the need for transfusions. Significant thrombocytopenia (platelet count < 10,000/mL), especially if bleeding is present, can be managed with transfusions of platelet concentrates. Recombinant thrombopoietin is available and will likely markedly reduce such transfusion needs.

Neutropenia (absolute neutrophil count < 1000/μL) is the most clinically relevant cytopenia because neutropenic fever and an increased risk of infection occur. *Fever > 38° C (100.4° F) in a granulocytopenic patient should be regarded as an emergency.* Evaluation of the neutropenic patient should include immediate cultures of blood, sputum, urine, and stool. The examination should focus on possible abscess sites (eg, retina, ears, rectum). Because the absence of neutrophils means that the expected signs of recognition of an abscess may not be evident, focal pain and tenderness may be clues to an incipient abscess.

A stable patient may be treated with an intensive outpatient regimen at many institutions, but in the absence of a defined program, hospitalization is needed. Treatment with broad-spectrum antibiotics should be started immediately after cultures of the blood, sputum, urine, and any suspicious skin lesions are obtained. If diffuse pulmonary infiltrates are present, the physician should include *Pneumocystis carinii* pneumonia in the differential diagnosis and institute empiric therapy, especially in patients with leukemia or lymphoma. In the presence of such infiltrates, the antibiotic regimen should include trimethoprim-sulfamethoxazole, an aminoglycoside, and a cephalosporin. In patients with an indwelling venous catheter, gram-positive infections are common and vancomycin should be added. If fever continues after 24 h, a semisynthetic penicillin (eg, ticarcillin) should be added. If fever continues for 72 to 120 h, a fungal etiology should be considered and amphotericin B should be added to the therapy program.

An important therapeutic addition during neutropenic sepsis or fever is cytokine therapy with granulocyte colony-stimulating factor (G-CSF—or alternatively granulocyte-macrophage colony-stimulating factor [GM-CSF]). G-CSF (5 μg/kg/day sc or by infusion) is the drug of choice and should be instituted at the onset of fever or sepsis.

OTHER COMMON ADVERSE EFFECTS

Enteritis from abdominal radiotherapy can be alleviated with antidiarrheal drugs. Mucositis from radiotherapy can preclude substantial oral intake and lead to malnutrition and weight loss. Simple measures (eg, use of analgesics and topical lidocaine before meals, a bland diet without citrus food or juices, avoidance of temperature extremes) allow the patient to eat and maintain weight. If these simple measures fail, enteral alimentation with a flexible plastic tube (Dobhoff) may be considered as long as the small intestine is functionally normal. In cases of mucositis and diarrhea or an abnormally functioning bowel, parenteral alimentation may be substituted. Pain may be a problem but can be treated with drugs, focal radiotherapy, or surgery (see Ch. 167). Similarly, depression must be recognized. Frank discussion of a patient's fears can often relieve anxiety; a growing armamentarium is now available for treatment of depression (see Ch. 189).

INCURABLE CANCER

A common misconception is that some cancers are untreatable. Although the cancer may be incurable, the patient can be treated. Treatment means more than the use of surgery, radiotherapy, or chemotherapy; it means the wise care of the patient. For patients whose cancers are not responsive to these modalities, use of an ineffective chemotherapy drug to be "doing something" to the cancer is poor medicine. Appropriate therapy for such patients (and for all cancer patients) includes nutritional support, effective pain management, relevant palliative care, and psychiatric and social support. Above all, the patient must know that the clinical team will not abandon him because specific therapy does not exist or has not been effective. Participation in well-controlled research trials, if available and appropriate, should be considered and discussed with the patient. Hospice or other related end-of-life care programs are important parts of cancer treatment. For more information pertaining to patients with incurable disease, see Ch. 294.